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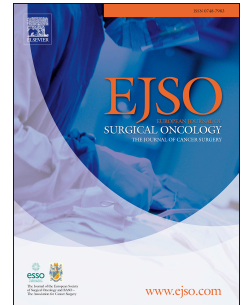
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ALPPS: the argument against

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The procedure of associating liver partition and portal vein ligation (ALPPS) was considered as a potential solution for patients with multifocal liver cancer to allow them to undergo extended resection safely. It was then subsequently designed as an alternative to either the need for pre-operative portal vein ligation or embolization, or alternatively to a two stage hepatic resection, which typically involved a significant delay of 4-6 weeks between the first and second stages. By clearing tumour from the left lateral section and ligating the branches of the portal vein to the intended resected liver combined with transecting the parenchyma, ALPPS was thought to result in accelerated liver regeneration of the future liver remnant while leaving a partially functioning hemiliver which provided sufficient metabolic contribution to prevent liver failure. This allowed a much shorter interval between first and second stages of typically 7 days to two weeks.

The ALPPS procedure emerged onto the surgical landscape in 2010 following an oral presentation of three such treated patients from Germany in a national meeting in Berlin and shortly after at the European and African HPB association meeting in Cape Town, South Africa in 2011. A formal paper was published in 2012¹. By the time of the next E-AHPBA meeting in Belgrade in 2013 this emergence of ALPPS had become more like a crash landing. The procedure had been widely adopted by enthusiasts and applied to a large number of clinical situations with numerous variations. Some of the presentations of series of patients undergoing ALPPS at that meeting described perioperative mortalities of up to 20%. Furthermore, case series were presented that included patients that left audience scratching their heads over why a conventional one stage resection was not performed without exposing the patient to the risk of an unnecessary two stage procedure. Since then there have been some very

welcome attempts to rationalize ALPPS including the creation of an international registry² and the provision of advice regarding patient selection and exclusion³. The way that ALPPS was introduced by the surgical community was unfortunate and the indications and patient selection today are much more conservative and considered than they were in 2013.

Given the concerns held by many over the way that ALPPS was introduced, with little apparent thought to trial or evaluation, it was even more concerning when numerous modifications of the procedure started to be described. This may be a valid style of experiential learning but coupled with high mortalities and morbidities it led to criticisms of surgical bluster, experimentation and risk taking. Unfortunately this further endorsed the view that many physicians hold of surgeons as lacking the ability to conduct or follow principles of evidence based medicine or research in the development of their practice.

The most common indication for ALPPS is multifocal colorectal hepatic metastases (CRM). It is worth considering how the outlook has changed for patients with CRM over the last two decades. The most significant change in the landscape of colorectal cancer has in my opinion been the development of truly effective chemotherapy strategies. The introduction of oxaliplatin and irinotecan based regimens along with biologics such as cetuximab and bevacizumab led to patients having much more consistent tumour responses than was ever seen with 5 Fluorouracil based regimens of twenty years ago. This in turn has led to more patients being able to reach a position where they can have liver surgery but also has allowed down-sizing of tumours to allow parenchymal sparing resections. An additional effect is that the urgency to manage colorectal hepatic metastases has been reduced and the overall timeline for management of patients has been extended. It is not uncommon now for patients to have several separate interventions of surgery or radiofrequency ablation interspersed with periods of first, second and third line chemotherapy over many years. Importantly all of this is done safely with low operative mortality and low mortality from chemotherapy associated complications. Most major units have operative mortality rates of 1-2% for patients undergoing surgery for colorectal

hepatic metastases. Even reoperation for colorectal liver metastases is not now associated with a high mortality and of course there are many second line chemotherapies and biologicals which can support surgical and ablative strategies. It is in this context that ALPPS should be viewed and this is one of the reasons that the high mortality rates presented in 2013 were found to be so shocking and unacceptable to many individuals.

In the early years of ALPPS it was clear that some patients were undergoing the procedure who did not need it. ALPPS has been performed for patients with an adequate future liver remnant for example undergoing right hepatectomy and leaving approximately 40% of liver. Similarly the procedure has been applied in the patient who could have undergone a more limited procedure such as mesohepatectomy or central liver resection to deal with right lobe tumours. In my opinion, it is not appropriate to consider ALPPS in these situations until ALPPS has an operative mortality approaching the rates for these procedures. The Italian registry has highlighted the high mortality of patients who have undergone ALPPS for cholangiocarcinoma and has suggested that a moratorium should be placed on ALPPS for this indication³. This view is endorsed by ALPPS International registry data which have shown a 48% mortality for patients with hilar cholangiocarcinoma undergoing ALPPS in expert centres⁴.

Looking at the causes of death of patients who die after ALPPS procedures, there is a common theme of struggling liver function and sepsis. There are some patients who fail to show adequate regeneration and yet still proceeded to the second stage with subsequent development of fatal liver failure. There are other patients who have followed a different pattern. One of the problems with the two stage procedure is that after the first stage perihepatic collections and bile leaks are common and reoperation in the second can stir up a septic response. It is well known that the combination of a small liver volume and sepsis can be a fatal combination⁵ and in some ways the process of ALPPS creates a perfect storm for this complication. Today analysis of experiences and outcomes of patients undergoing ALPPS⁶ has allowed the development of a 'futility' score

which is useful in determining which patients should proceed to second stage and those where discretion should be exercised⁷.

The ALPPS procedure was thought to supercharge liver regeneration but is this really the case? Evidence from comparative studies of kinetic growth rates of the liver show that a much faster kinetic growth rate is seen in the future liver remnant of patients with ALPPS compared with portal vein ligation or portal vein embolization. Data from the Mayo clinic show that the kinetic growth rate of the FLR in ALPPS is the same as healthy liver after a liver resection or the same as regeneration after living donor liver donation or transplantation⁸. Thus there is a limited effect of ALPPS in terms of liver regeneration compared with other types of liver resection. It is probably important to acknowledge this when considering patient safety and the timing of second stage procedures. What has become very clear is that a failure to exhibit effective regeneration in the future liver remnant is predictive of poor outcome from ALPPS⁹.

Many of my personal concerns around ALPPS were to do with the way it was introduced and the resulting poor case selection leading to high mortality and morbidity [for many patients]. It is pleasing to see that more contemporary reports are clarifying selection criteria both in embarking on the procedure and, in particular, in defining who should proceed to the second stage. It is also gratifying that contemporary reports of ALPPS show improvements of morbidity and mortality for patients. It is reasonable to ask therefore where ALPPS should fit into the surgical armamentarium today. There are certain patients in whom there is a risk of tumour escape if a two stage procedure is performed or preoperative portal vein embolization strategies are used. Perhaps greater thought should be given to key questions concerning individual patients and their suitability for ALPPS and I have suggested some of these in Figure 1. There may be a role for ALPPS in these situations if there is no clear alternative surgical strategy. For the moment the conclusion of the recently released meta-analysis of outcomes following ALPPS concludes *"ALPPS is associated with greater future liver remnant hypertrophy and a higher rate of completion of stage 2, but this may be at the price of greater morbidity and mortality."*¹⁰

One of the key future developments for liver surgery has to be to standardize measurement of the volume function relationship which will permit a more safe approach to liver surgery in whatever form this is undertaken.

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Legend Figure 1

Suggested pathway for decision making for patient selection and progression of ALPPS or procedures requiring portal vein embolization or ligation.

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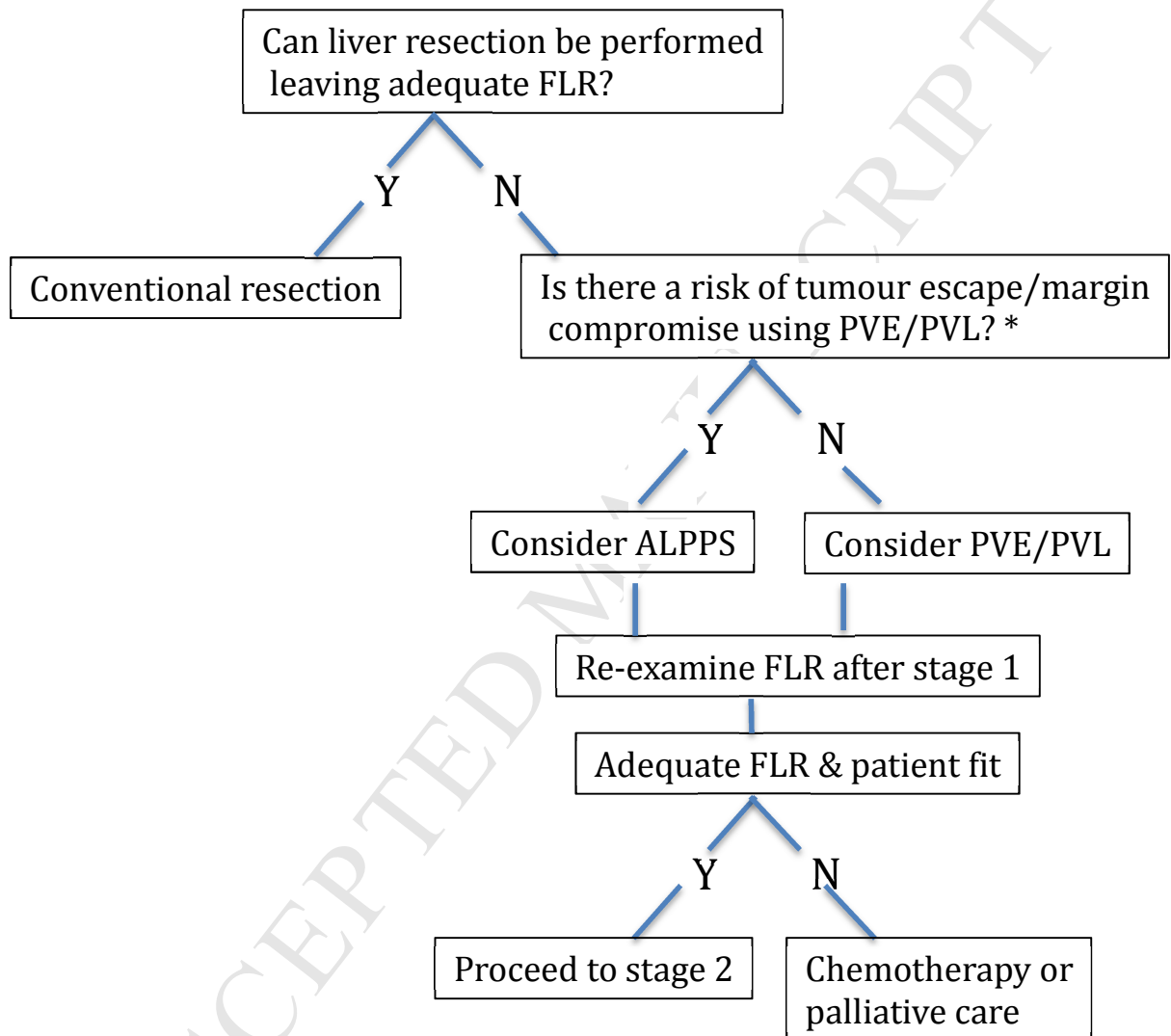
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Figure 1

Suggested pathway for decision making for patient selection and progression of ALPPS or procedures requiring portal vein embolization or ligation.



* Patients with hilar cholangiocarcinoma should not undergo ALPPS but should be managed using approaches using PVE/PVL if FLR is considered inadequate.